Clozapine Underutilization: Addressing the Barriers

Deanna L. Kelly, Pharm.D., BCPP
Professor of Psychiatry
Director, Treatment Research Program
Maryland Psychiatric Research Center
University of Maryland School of Medicine
Overview:
Summary of Project Purpose

• Clozapine is a medication that exhibits unique efficacy and effectiveness for those with serious mental illness, despite side effects that present challenges to its use.

• These challenges have evolved into a set of barriers that discourage the use of clozapine.

• Proven approaches using interprofessional models of care can help meet the needs of patients receiving clozapine.

• State and local government, federal agencies, academic medical centers, prescribers and others all have vital roles to play in increasing access to clozapine.

• NASHMPD has commissioned a White Paper to help rectify the clozapine situation nationally.
NASMHPD Workgroup

• Raymond C. Love, PharmD, BCPP, FASHP
• Deanna Kelly, PharmD, BCPP
• Oliver Freudreich, MD, FAPM
• MacKenzie A. Sayer, BS
• Kathy Sanders, MD
• Andrew J. McLean MD, MPH
• Dale K. Adair, MD
• Brian Hepburn, MD
• Aaron J. Walker, MPA
• Stuart Yael Gordon, JD
Efficacy of Clozapine

Clozapine is the most effective antipsychotic for patients with schizophrenia who do not respond to treatment with first or second-generation antipsychotics.
• Several large effectiveness studies suggest that clozapine:
  – averages significantly greater time to treatment discontinuation [9]
  – is associated with significantly greater patient perceived ratings [10]
  – is associated with significantly greater clinician ratings [11]
Importance of Clozapine

• The Schizophrenia Patient Outcomes Research Team (PORT) [12] recommends that patients with persistent positive symptoms of schizophrenia receive an adequate trial of clozapine.

• More recent guidelines recommend clozapine after two failed antipsychotic trials:
  – Harvard South Shore Program Algorithm [13]
  – British Association for Psychopharmacology Guidelines [14]

• Early use is critical for young patients with schizophrenia who are treatment-refractory and in whom only clozapine offers a chance for improvement and course stabilization as the basis for recovery [16]
Broad Range Effectiveness

- Clozapine may have utility for a variety of other disorders and conditions
  - treatment of hostility and aggression \[17\]
  - treatment-resistant bipolar disorder \[18\]
  - psychogenic polydipsia/hyponatremia \[19\]
  - Parkinson Disease Psychosis \[20\] and psychosis in Lewy-Body dementia \[21\]
  - Borderline Personality Disorder \[22\]
  - tardive dyskinesia (TD) \[23\]

- Growing evidence also suggests clozapine may be an option in youth with early onset schizophrenia \[24\]

- Clozapine is the only antipsychotic with a Food and Drug Administration approval for suicidality and it has the lowest mortality rate among all antipsychotic treatments \[25\]

- Clozapine use has been found to be cost effective \[26\] and should not be put off from use after 2 trials \[27\]
Risk to Benefit Profile

- Clozapine use is associated with a variety of side effects, some of which are potentially serious
  - **Common side effects include**: hypersalivation, tachycardia, enuresis, sweating, eosinophilia, metabolic syndrome and constipation [28-30, 39]
  - **Serious but rare side effects include**: myocarditis (3% risk) [31], cardiomyopathy (0.02-0.1% risk), [32] seizures (1-3% risk), [33] and severe neutropenia (0.05-0.86%) [34-38]
  - Severe neutropenia risk has led the FDA to mandate regular blood draws to monitor the absolute neutrophil count (ANC)
Risk to Benefit Profile (Continued)

• The decision to use clozapine requires a thorough consideration of both its risks and benefits, a thoughtful patient centered approach and a system that facilitates safe and appropriate use [40]

• Often ignored in risk-benefit discussions are the medical risks of not using clozapine
  – Other antipsychotics and polypharmacy have medical risks [41]
  – Poorly treated psychiatric illness can complicate medical treatment
Underuse of Clozapine

- Prescribed infrequently in the US: considerably lower than the estimated prevalence of treatment-resistant schizophrenia[42-46]
- Use of clozapine declining from 11% of all antipsychotic prescriptions in 1999, to about 4% in 2008 [25]
- Used more frequently in other countries (e.g., 36-38% in Australia, 26% in China, 20-30% in Taiwan) [43, 47]
- Polypharmacy is more frequently prescribed than clozapine monotherapy, suggesting that many clinicians choose unproven strategies often over clozapine [48, 49]
- Only 6 states prescribe clozapine > 10% while 9 states use clozapine less than 3% of all antipsychotics [50]
- Frequently there is a delay starting clozapine. Data shows often years before clozapine and many more trials than 2 failed prior to trying clozapine [51, 52]
Patient’s Attitudes to Clozapine

- N=1284, 27 clozapine clinics in UK
  - 86% feel better on clozapine
  - 89% prefer clozapine to other antipsychotics
  - 87% think advantages outweigh disadvantages
  - 28% rank frequent blood work as biggest disadvantage
Provider Attitudes to Clozapine

• Psychiatrists overestimate real risk of severe neutropenia (agranulocytosis)
  – 23% think risk is >1%
  – 67% don’t know risk is greatest in first 6 months
  – Psychiatrists are 5X more likely than patients to rate agranulocytosis risk as most problematic issue with clozapine
Overcoming Barriers to Use

- Prescriber knowledge and comfort
- Patient and family knowledge and comfort
- Clozapine clinics
- Hospitals and formularies
- Registration in ClozapineREMS
- Point of care monitoring
- Pharmacogenetic testing
Overcoming Barriers to Use

• Assistance in clozapine initiation
• Use in correctional systems and forensic settings
• Managing side effects
• Improving transitions of care
• Suicide and emergency hotlines
• Working with Medicaid and managed care companies
• Blood draw ease and monitoring
Highest Ranking Barriers to Clinical Use

Side effects
- Cardiomyopathy
- Metabolic syndrome
- Agranulocytosis

Clinical
- Need for closer monitoring
- Regular blood work
- Non-adherence to blood work

Non-clinical
- Lack of centralized system
- Time spent on admin. tasks
- Lack of admin. structure in practice

N=277/860 (32%) psychiatrists responded, N=255 available for analysis

Mean score: 1= not a barrier; 5= a significant barrier.
Neutropenia in People of African Descent

- Normative WBC ranges established in Caucasians
- Lower WBC and ANC in African vs. European descent
- Benign Ethnic Neutropenia (BEN)
  - the occurrence of neutropenia, defined by normative data in white populations, in individuals of other ethnic groups who are otherwise healthy and who do not have repeated or severe infections
- No greater risk of severe neutropenia (agranulocytosis)
- Linked to variant of Duffy Antigen for Receptor Chemokine (DARC) Gene: ANC difference related to this factor is sufficient to explain the observed racial difference
- New guidelines came out in 2015 allowing for treatment in patients with BEN
- Studies underway to provide data to help in modifying guidelines

[56, 57, 58]
# Mean ANCs by Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>%</th>
<th>ANC x 10^6 cells/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY -/-</td>
<td>4,111</td>
<td>68.5</td>
<td>2459</td>
</tr>
<tr>
<td>FY +/-</td>
<td>1,647</td>
<td>27.4</td>
<td>3982</td>
</tr>
<tr>
<td>FY +/+</td>
<td>247</td>
<td>4.1</td>
<td>4013</td>
</tr>
</tbody>
</table>

Epidemiologic Cohort of 6,005 Self-Identified African Americans
RESULTS OF THE NASMHPD WORKGROUP

Clozapine Recommendations
Prescribers

• Prescribers of clozapine should establish links with primary care practices to assist in the management of side effects that may emerge during treatment with clozapine

• Prescribers should continually seek to improve knowledge base with lifelong learning on clozapine treatment

• Less experienced prescribers should establish links with more experienced prescribers who can assist them in addressing issues that arise during clozapine treatment
Acute Care and Psychiatric Hospitals

• All acute care and psychiatric hospitals should have clozapine on their formulary as an essential medication
• All acute care and psychiatric hospitals should have policies and procedures to facilitate the safe and appropriate use of clozapine
• All acute care hospitals should have access to appropriate staff or resources that allow continuation of clozapine on an inpatient basis when appropriate
• All acute care hospitals should establish a policy that discharges patients on clozapine if:
  – they were taking clozapine prior to admission,
  – they were exhibiting a therapeutic response to clozapine, and
  – there is no contraindication to the use of clozapine upon discharge
Academic Scientists and Pharmaceutical Research Programs

- Neuroscience and pharmacologic research should focus on the molecular underpinnings of clozapine’s actions in order to facilitate the development of agents which share clozapine’s efficacy while eliminating its worse side effects.

- Research should also focus on improving the understanding of clozapine induced blood dyscrasias, eliciting factors associated with a positive response to clozapine and discovering biomarkers that could improve the risk-to-benefit ratio for treatment with clozapine.

- Systems research should focus on demonstrating clozapine’s cost effectiveness in various systems of care including forensics, best practices for interdisciplinary teams managing patients receiving clozapine, developing novel practice and service models and establishing the effectiveness of prevention strategies for clozapine-associated weight gain and metabolic effects.
• Technological support should include the development of point-of-care testing devices to perform hematologic monitoring for those receiving clozapine

• Research should be focused to aid the FDA in modifying prescribing and monitoring guidelines for those receiving clozapine
Local and State Health Authorities

- Every public health system of care should have a system that provides ready access to clozapine, provides appropriate safety monitoring of patients receiving it and encourages prescribers to consider its use when appropriate.

- Mental health authorities should consider establishing model programs for the initiation and monitoring of clozapine patients and consider offering evidence-based recommendations for addressing metabolic side effects and other emergent side effects.

- Mental health authorities should establish mechanisms for the initiation of clozapine in outpatients such as designated beds in respite care or sites offering 24 hour supervision or clozapine clinics with this capacity and expertise.
Local and State Health Authorities Continued

• Academic centers in consultation with state or local mental health authorities should establish interdisciplinary consultation centers for community providers involved in the management of patients receiving clozapine.

• Mental health authorities should develop community specific systems for laboratory monitoring of patients receiving clozapine that may include the use of Assertive Community Treatment (ACT) teams, transportation systems, visiting phlebotomists, pharmacy based phlebotomy or other solutions.

• Mental health authorities should develop population management tools to facilitate and monitor transitions of care, help assure continuation of treatment and reduce interruptions in the treatment of patients receiving clozapine.
Payers

- Payers should develop payment mechanisms that recognize the complexity of managing patients receiving clozapine including:
  - enhanced payment mechanisms for prescribers;
  - payment mechanisms for nurses, pharmacists and social workers participating in interdisciplinary clozapine teams;
  - payment for telemedicine systems to provide consultation for community health professionals managing clozapine patients
  - payment for transportation for patients for laboratory monitoring and/or payments for home visits for phlebotomy
Payers
(Continued)

• Clozapine should be a Tier 1 preferred medication (or its equivalent) on the formularies of all state Medicaid programs, Medicare prescription drug programs, pharmacy benefit/managed care programs contracting with state Medicaid programs and other payers of pharmacy benefits

• Payers should encourage the development, adoption of and reimburse for Medication Therapy Management (MTM) services for patients receiving clozapine
Every correctional health care system should have a system that provides ready access to clozapine or establishes mechanisms for referral of inmates who are appropriate for treatment with clozapine.

Every correctional health care system should have policies and procedures to facilitate the safe and appropriate use of clozapine.

Every correctional health care system should provide appropriate safety monitoring of patients receiving clozapine.
Providers of Continuing Education for Health Professionals

• Health professional organizations and continuing education providers should develop and offer interdisciplinary continuing education programs on the use of clozapine that include physicians, pharmacists, nurses, social workers and other health care providers
National Efforts

National efforts should focus on the development and dissemination of the following types of toolkits and information related to clozapine:

– Sample informed consent form for clozapine;
– Discussion paper on shared decision making;
– Forms for monitoring specific side effects;
– Patient and family education materials;
– Checklists for establishing a clozapine clinic including materials on interdisciplinary roles in the management of patients receiving clozapine, establishing pharmacy linkages for patients receiving clozapine, options for hematologic testing, potential funding mechanisms or models for clozapine programs and models for a clozapine consultation service including interdisciplinary telehealth models;
– Reference links to educational programs regarding the use of clozapine
National Efforts Continued

- National efforts should continually evaluate the ClozapineREMS Program in order to assure that it facilitates clozapine use and does not present unintended barriers to use.
  - This evaluation should consider scientific evidence and analyze data trends that might inform changes in clozapine monitoring guidelines such as less frequent ANC monitoring, genetic testing that dictates less stringent hematologic monitoring, or elimination of ANC monitoring in patient groups who have minimal risk of severe neutropenia (i.e., African descent).
- National efforts should focus on work with relevant stakeholders to explore the use of the ClozapineREMS Program as a population management tool that could be used by state systems to facilitate and monitor transitions of care, help assure continuation of treatment and reduce interruptions in treatment in patients receiving clozapine.
Technology Development

- Telehealth and call center technology should be used to provide access to professionals who can provide consultation on the complexities of clozapine use.
- The technology of the ClozapineREMS registry should be harnessed to improved facilitate and monitor transitions of care and reduce interruptions in treatment for those receiving clozapine.
- Establishment of a dynamic, web-based source of information educational programs providing information on delivery models, patient monitoring, patient and family education and provider education would assist all who might serve potential recipients of clozapine.
- Point-of-care testing should be developed to assist in monitoring of those receiving clozapine.
- Biomarker testing to improve the predictability of response to clozapine and the risk for specific adverse effects should be developed.
Conclusions

• Clozapine is a superior medication for the treatment of refractory schizophrenia and may be effective for a wide spectrum of other indications

• Clozapine is underused due to a variety of barriers related to the drug and its properties, the health care system, regulatory requirements and reimbursement issues

• This white paper provides the framework for addressing these barriers and recommending strategies for the entire health care system to consider

• If access to clozapine is improved, millions of patients could benefit. In turn their improved care could substantial cost savings to the entire health care system
References


54. Adapted from: Hodge K and Jesperson S. *Side-effects and treatment with clozapine: a comparison between the views of consumers and their clinicians*. Int J Mental Health Nurs 2008;17:2-8


